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Health and Environmental
Effects Profile for Dinitrocresols

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16. ABSTRACT The Health and Environmental Effects Profile for <u>Dinitrocresols</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Dinitrocresols</u> has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for <u>4,6-dinitrocresol</u> is 0.1×10^{-3} mg/kg/day for inhalation exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for <u>4,6-dinitro-o-cresol</u> is <u>100</u> . Existing data are insufficient to determine an RQ value for <u>2,6-dinitro-p-cresol</u> .		
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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR DINITROCRESOLS

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA docket.

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EXECUTIVE SUMMARY

The dinitrocresols are yellow crystalline compounds at ambient temperatures (Hawley, 1981; Weast, 1985). 4,6-Dinitro-o-cresol is used as an insecticide and herbicide (Worthing and Walker, 1983) and as a free-radical polymerization inhibitor (Kuney, 1985); its uses as a pesticide are being replaced by its homologs and by 2,4-dinitro-6-sec-butylphenol, which is less expensive and more effective (U.S. EPA, 1985a). 2,6-Dinitro-p-cresol is used as a chemical intermediate and as a polymerization inhibitor (Kuney, 1985; Hawley, 1981).

Sufficient experimental data were not available to predict the exact fate of the dinitrocresols in water; however, photolysis and oxidation appear to be two mechanisms by which the dinitrocresols may be measurably removed from sunlit waters. Although the biodegradability of 4,6-dinitro-o-cresol has been demonstrated in mixed bacterial cultures (Chambers et al., 1963), in activated sludge (Patterson and Kodukala, 1981) and in various pure culture studies (McCormick et al., 1976; Nehez et al., 1977a; Hamdi and Tewfik, 1970; Gundersen and Jensen, 1956; Jensen, 1966; Merenyuk, 1974; Wallnoefer et al., 1978; Tewfik and Evans, 1966), the significance of biodegradation in natural waters cannot be predicted with certainty from the available data. Hydrolysis, volatilization, bioaccumulation and adsorption are not expected to be important processes, although adsorption to clay minerals may have some significance (Callahan et al., 1979).

Dinitrocresol present in the ambient atmosphere is expected to be rapidly removed by reaction with OH radical. Based on a theoretically calculated rate constant, the half-life of 4,6-dinitro-o-cresol in the atmosphere, with respect to OH radical, has been calculated to be ~8 hours (U.S. EPA, 1986a). Photolysis may have some significance as an atmospheric removal sink.

4,6-Dinitro-o-cresol usually disappears from soil within a few weeks to 2 months (Callahan et al., 1979) when applied as a herbicide. The microbial degradation of 4,6-dinitro-o-cresol in soil has been demonstrated (Jensen, 1964; Ammon and Jaeggi, 1981); a repeated application of 4,6-dinitro-o-cresol to a soil resulted in a shorter decomposition time, which may be due to microbial adaptation (Gundersen and Jensen, 1956). Based on K_{oc} estimations from regression equations, 4,6-dinitro-o-cresol is expected to have moderate to low soil mobility, which suggests that some leaching can occur. Leaching is expected to be greatest in sandy soils and minimal in clay soils.

4,6-Dinitro-o-cresol has been detected in various industrial wastewater effluents (U.S. EPA, 1980a; Shackelford and Keith, 1976; McMahon, 1983) and in the water-sediment soil complex at the Love Canal (Hauser and Bromberg, 1982). No water monitoring data were located for 2,6-dinitro-p-cresol. Exposure of 4,6-dinitro-o-cresol to the water environment may result from direct pesticidal applications or by pesticide leaching or runoff. No pertinent data were located on the presence or absence of dinitrocresol residues in United States food. Persons at the greatest risk to inhalation and dermal exposure to 4,6-dinitro-o-cresol include workers manufacturing, formulating or applying the pesticide as an aerosol (U.S. EPA, 1980a). No ambient atmospheric monitoring data were found for any of the dinitrocresols.

Limited information is available concerning toxicity of dinitrocresols to aquatic organisms. Most of the data pertained to 4,6-dinitro-o-cresol. The lowest reported acutely toxic concentration was 0.066 mg/L, a 96-hour LC_{50} for rainbow trout (Johnson and Finley, 1980). Salmonid fishes and bluegills appeared to be more sensitive to 4,6-dinitro-o-cresol than minnows (see Table 5-1). Among invertebrates, the lowest reported acutely toxic concentration was 0.012 mg/L 4,6-dinitro-o-cresol, the toxicity threshold

for the ciliate protozoan Uronema parduczi (Bringmann and Kuehn, 1981). The LC_{50} values for 2,4-dinitrocresol (LeBlanc, 1980) and 4,6-dinitro-o-cresol (Bringmann and Kuehn, 1977) indicated a similar level of toxicity to Daphnia magna. No additional data for dinitrocresols other than the 4,6-isomer were found and no data for marine fish and invertebrates were located.

Slooff and Canton (1983) provided chronic toxicity data for unspecified dinitrocresols. Chronic effects in several fish and invertebrates generally occurred at concentrations close to those causing acute toxicity. The lowest threshold in this study was 0.032 mg/L, a NOEC for reproductive effects in snails.

Among the plant species tested, the most sensitive was the blue-green alga, Microcystis aeruginosa, with a toxicity threshold of 0.15 mg/L (Bringmann and Kuehn, 1978).

Pertinent data regarding the pharmacokinetics and metabolism of 2,6-dinitro-p-cresol could not be located in the available literature as cited in the Appendix. 4,6-Dinitro-o-cresol is rapidly absorbed through the skin, the respiratory system and the gastrointestinal tract (King and Harvey, 1953a). Rats absorbed >90% of an orally administered dose within 7 hours. Based on blood elimination curves it appears that humans and rats, but not rabbits, may accumulate some 4,6-dinitro-o-cresol because of the ability of the compound to bind to plasma proteins (King and Harvey, 1953b). Half-lives for elimination were 154 hours for humans, 27 hours for rats and 6.6 hours for rabbits. Data for the rat using the 3,5-isomer indicated little accumulation in the tissues (Parker et al., 1951). In rabbits, 4,6-dinitro-o-cresol was metabolized primarily to 6-amino-4-nitro-o-cresol and hydroxy group conjugates (Smith et al., 1953; Truhaut and DeLavaur, 1967). These metabolites were excreted in the urine. Elimination of the compound occurs

more rapidly following injection rather than oral administration, and excretion patterns of humans vs. experimental animals are substantially different.

Pertinent data regarding the carcinogenicity of isomers of dinitrocresol could not be located in the available literature; the isomers have not been scheduled for testing by the National Toxicology Program (NTP, 1986).

Inconsistent results have been reported for mutagenicity testing. Anderson et al. (1972) reported negative results for 4,6-dinitro-o-cresol when tested without activation in eight strains of S. typhimurium; however, positive results without activation were reported for 4,6-dinitro-o-cresol in S. typhimurium strains TA98, TA100 and TA1538 and for 2,6-dinitro-p-cresol in strain TA100; addition of S-9 reduced the mutagenicity (Sundvall et al., 1984). Nishimura and Oshima (1983) and Nishimura et al. (1982) reported mutagenicity for 4,6-dinitro-o-cresol in strain TA98 in the presence of metabolic activation, whereas Somani et al. (1981) reported a positive response without metabolic activation in strain TA100 but not TA98. Positive responses were observed for a herbicide containing 50% 4,6-dinitro-o-cresol (Krezonit E) when tested in human lymphocytes, mouse bone marrow (Nehez et al., 1977b, 1978a,b, 1980, 1984), dominant lethal test in mice (Nehez et al., 1978c) and recessive lethal test in Drosophila (Haberzettl and Mueller, 1979; Mueller and Haberzettl, 1979).

No embryotoxic or teratogenic effects were observed in the offspring of DBA or ABH-J mice treated orally or intraperitoneally with 8-15 mg/kg of the herbicide (Krezonit E) containing 50% dinitro-o-cresol during gestation (Nehez et al., 1981). Increases in chromosome aberrations of the embryos were observed when Krezonit E was administered orally to CFLP mice in trimester I.

Information regarding the effects of oral administration of 4,6-dinitro-o-cresol to humans is available since this compound was used in the treatment of obesity. Toxic effects, which included elevated BMR, excessive sweating, thirst, fatigue, decreased appetite and greenish-yellow conjunctiva, were reported when 0.35-1.5 mg/kg/day was ingested for periods up to 9 weeks (Plotz, 1936; Ibrahim et al., 1934). Similar but less pronounced symptoms developed when the compound was given in similar dosages for a few days (Harvey et al., 1951; Dodds and Robertson, 1933). When the compound was given at 3 mg/kg/day, marked signs of toxicity developed and the BMR was elevated by 100% on the 4th day of treatment. These effects disappeared when treatment was discontinued (Dodds and Robertson, 1933). Deaths from overdoses and blindness resulting from formation of bilateral cataracts have been reported (NIOSH, 1978; U.S. EPA, 1980a). Neither dose-response information nor duration of treatment associated with cataract formation was specified in the literature. In a case report by Quick (1937), cataract formation resulting in blindness was reported in a woman who ingested the compound for 3 years at an unspecified dosage.

When 4,6-dinitro-o-cresol was administered in the diets of rats at 0, 0.01, 0.02, 0.05 and 0.1% for periods up to 181 days, no compound-related effects were observed at the 0.01% level. At the 0.02% level, significant decreases in weight gain, food consumption and organ weight occurred. Marked toxicity developed at the 0.05 and 0.1% levels (Spencer et al., 1948). Ambrose (1942) reported no effects at a level of 62.5 ppm in rats fed the compound for 105 days; however, at a level of 125 ppm, 60% of the rats died. Many compound-related effects were observed in rats at dietary levels of 100, 200 and 400 ppm for 90 days (Den Tonkelaar et al., 1983).

Effects on mortality, food intake and efficiency, growth, hematological changes, changes in clinical chemical parameters in blood and urine, and changes in absolute and relative organ weights were noted at levels ≥ 100 ppm and were more severe at the highest level. The only effects noted when the compound was given at 50 ppm was the presence of ketones in the urine, and a reduction in pyruvate, T_3 and T_4 levels. Pyruvate and T_3 were reduced in a dose-related manner (Den Tonkelaar et al., 1983). Cataract formation was not observed or mentioned in the animal studies (Spencer et al., 1948; Den Tonkelaar et al., 1983).

Case reports from occupational exposure have shown the compound to be toxic to humans when inhaled (NIOSH, 1978; U.S. EPA, 1980a); however, few reports link effects with exposure levels. In general, symptoms from inhalation exposure appear to be similar to those resulting from oral exposure. Cataract formation has not been documented in humans or animals as a result of inhalation exposure.

Three ADIs for 4,6-dinitro-o-cresol were recommended for consideration. Two were derived from the TLV of 0.2 mg/m^3 , using a breathing volume of $10 \text{ m}^3/8\text{-hour workday}$, expanding over a 7-day week and using an uncertainty factor of 100. In one approach, an absorption factor of 0.5 was used, which resulted in an ADI of $0.1 \times 10^{-3} \text{ mg/kg/day}$. In another approach, gastrointestinal and pulmonary absorption were assumed to be equal, which resulted in an ADI of $0.2 \times 10^{-3} \text{ mg/kg/day}$. An ADI of $0.35 \times 10^{-3} \text{ mg/kg/day}$ was also derived based on the lower range of oral doses (0.35 mg/kg/day) that had been prescribed for patients for weight reduction, using an uncertainty factor of 1000. The dose of 0.35 mg/kg/day was considered a LOAEL for elevated BMR, excessive sweating, fatigue and thirst, discoloration of the conjunctiva and possibly cataract formation. This dose and effects were

also used as the basis for the RQ of 100. It is proposed that the most conservative estimate, 0.1×10^{-3} mg/kg/day be utilized as an interim ADI.

Data were insufficient to derive an ADI and an RQ for 2,6-dinitro-p-cresol. Because no data regarding the carcinogenicity of these compounds were available, they are placed in CAG Group E.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BMR	Basal metabolic rate
BUN	Blood urea nitrogen
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
EC ₅₀	Concentration effective to 50% of recipients
IgG	gamma-G globulin
IgM	gamma-M globulin
K _{oc}	Soil sorption coefficient
K _{ow}	Octanol/water partition coefficient
LC ₅₀	Concentration lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
RQ	Reportable quantity
RV _d	Dose-rating value
RV _e	Effect-rating value

LIST OF ABBREVIATIONS (cont.)

SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposed level
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The structures, CAS Registry numbers, molecular weights and empirical formulas of the individual dinitrocresols are listed in Table 1-1. The general CAS number for dinitrocresol (unspecified isomer) is 1335-85-9.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Selected physical properties of the dinitrocresol isomers are listed in Table 1-2. 4,6-Dinitro-o-cresol is soluble in alcohol, ether and acetone (Weast, 1985). 4,6-Dinitro-o-cresol is similar to other dinitrophenols in that it readily forms water-soluble salts with sodium, potassium and ammonium (Metcalf, 1981). It readily reduces to 6-amino-4-nitro-o-cresol and forms complexes with amines, hydrocarbons and phenols (Martin and Worthing, 1977).

1.3. PRODUCTION DATA

The Sherwin-Williams Co. (Chicago, IL) is the only U.S. manufacturer of 2,6-dinitro-p-cresol (SRI, 1985). In 1977, Sherwin-Williams produced between 10 and 100 thousand pounds of the chemical (U.S. EPA, 1977).

Blue Spruce Co. (Millington, NJ) and CPS Chemical Co. (Old Bridge, NJ and West Memphis, AR) are cited as current manufacturers of 4,6-dinitro-o-cresol (SRI, 1985). No current production volumes are available. Production data for 1977 are listed in Table 1-3.

It has been suggested that 2,6-dinitro-p-cresol is formed as a minor product during 4,6-dinitro-o-cresol production (Harvey, 1953). 4,6-Dinitro-o-cresol is manufactured by the sulfonation of o-cresol followed by controlled nitration (Martin and Worthing, 1977).

TABLE 1-1

The Synonyms, Empirical Formulas, CAS Numbers and Structures for Dinitrocresols

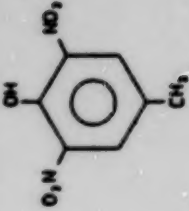
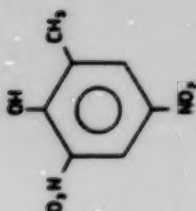
Synonyms	Empirical Formula	Molecular Weight	CAS Registry Number	Structure
2,6-Dinitro-p-cresol 4-methyl-2,6-dinitrophenol DNPC Victoria Orange Victoria Yellow	$C_7H_6N_2O_5$	198.15	509-93-8	
4,6-Dinitro-o-cresol 2-methyl-4,6-dinitrophenol DNOC Antinonin Sinox	$C_7H_6N_2O_5$	198.15	534-52-1	

TABLE 1-2
Physical Properties of the Dinitrocresols

Property	2,6-Dinitro-p-cresol	4,6-Dinitro-o-cresol
Description	light yellow crystalline solid ^a	yellow solid ^a
Melting point, °C	80-81 ^c	86.5 ^b
Boiling point, °C	NR	NR
Water solubility, ppm	290 at 18°C ^c	130 at 15°C ^d
Vapor pressure, mm Hg	NR	1.05x10 ⁻⁴ at 25°C ^d 0°C ^e
pKa	NR	4.46 ^e 4.35 ^f
Log K _{ow}	2.564 (calculated) ^g	2.564 (calculated)
Air conversion factor	NR	1 mg/m ³ = 0.12 ppm ^h

^aHawley, 1981

^bWeast, 1985

^cHarvey, 1953

^dWorthing and Walker, 1983

^eCessna and Grover, 1978

^fPearce and Simkins, 1968

^gU.S. EPA, 1986a

^hVerschueren, 1983

NR = Not reported

TABLE 1-3
Production Data for 4,6-Dinitro-o-cresol*

Company/Location	Manufacturer or Importer	Production Volume (pounds)
Alpine Labs./ Bay Minette, AL	manufacturer	0.1-1.0 million
FMC Corp./ Richmond, CA	importer	10-100 thousand
DuPont/ Wilmington, DE	importer	1-10 thousand
Henley and Co./ New York, NY	importer	confidential

*Source: U.S. EPA, 1977

1.4. USE DATA

4,6-Dinitro-o-cresol is strongly phytotoxic and is used as a dormant spray insecticide, especially for fruit trees or on waste ground to kill locusts (Worthing and Walker, 1983); it is ovicidal to certain insects and spider mites. As a dormant spray, it is used in the form of the sodium salt, while the free phenol has been used as an oil spray for grasshoppers and as a dust barrier for chinch bugs (Metcalf, 1981). 4,6-Dinitro-o-cresol is also used as a contact herbicide for the control of broad-leaf weeds in cereals and for the pre-harvest desiccation of potatoes and leguminous seed crops (Worthing and Walker, 1983). 4,6-Dinitro-o-cresol is being replaced in its pesticidal uses by its homologs and by 2,4-dinitro-6-sec-butylphenol, which is less expensive and more effective (U.S. EPA, 1985a). 4,6-Dinitro-o-cresol is also used as a free-radical polymerization inhibitor (Kuney, 1985).

2,6-Dinitro-p-cresol is used as an intermediate for fungicides, plastic and coating polymers, biologically active and other compounds, and as a polymerization inhibitor for vinyl aromatic compounds (Kuney, 1985). It is also used as a parent compound for intermediates, dyes and pharmaceuticals (Hawley, 1981).

1.5. SUMMARY

The dinitrocresols are yellow crystalline compounds at ambient temperatures (Hawley, 1981; Weast, 1985). 4,6-Dinitro-o-cresol is used as an insecticide and herbicide (Worthing and Walker, 1983) and as a free-radical polymerization inhibitor (Kuney, 1985); its uses as a pesticide are being replaced by its homologs and by 2,4-dinitro-6-sec-butylphenol, which is less expensive and more effective (U.S. EPA, 1985a). 2,6-Dinitro-p-cresol is used as a chemical intermediate and as a polymerization inhibitor (Kuney, 1985; Hawley, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Experimental hydrolysis data for the dinitrocresols could not be located in the available literature as cited in the Appendix. Since aromatic nitro compounds and phenols are resistant to hydrolysis (Neely, 1985), hydrolysis is not expected to be an important fate mechanism. Callahan et al. (1979) suggested that 4,6-dinitro-o-cresol may be susceptible to some hydrolysis while sorbed to clay minerals, but experimental data are not available.

2.1.2. Oxidation. Mabey et al. (1981) theoretically calculated the rate constants for the aquatic reaction (at 25°C) between 4,6-dinitro-o-cresol and peroxy radical ($RO_2^\cdot$) or singlet oxygen to be 5×10^5 and 3×10^4 $M^{-1} \text{ hr}^{-1}$, respectively. Assuming the concentrations in natural waters are $10^{-18} M$ $RO_2^\cdot$ and $10^{-12} M$ singlet oxygen, the half-life of 4,6-dinitro-o-cresol with respect to $RO_2^\cdot$ is calculated to be 58 days and, with respect to singlet oxygen, 2600 years.

The atmospheric rate constant for the reaction between 4,6-dinitro-o-cresol and OH radical has been calculated to be $3 \times 10^{-11} \text{ cm}^3/\text{molecule-sec}$ at 25°C (U.S. EPA, 1986a). Using the method of Guesten et al. (1981), the atmospheric rate constant can be used to estimate an aquatic rate constant of $1 \times 10^{10} M^{-1} \text{ sec}^{-1}$. Assuming an aquatic OH radical concentration of $10^{-17} M$, a half-life of 80 days is calculated.

The combined oxidation rates of reactions of OH and $RO_2^\cdot$ radicals with 4,6-dinitro-o-cresol can be used to calculate a half-life of 34 days, which suggests that aquatic oxidation may be important.

2.1.3. Photolysis. At a pKa of 4.46 (Cessna and Grover, 1978), 4,6-dinitro-o-cresol will exist substantially as an anion in environmental surface

waters. The UV absorption spectrum of 4,6-dinitro-o-cresol in dioxane exhibits a maximum at 265 nm, which extends beyond 400 nm (Callahan et al., 1979); in aqueous NaOH, there is a strong maximum at 372 nm (Callahan et al., 1979). Similarly, 2,6-dinitro-p-cresol exhibits a maximum at 446 nm in NaOH (Harvey, 1953). These UV absorption data indicate that the dinitro-cresols are potentially susceptible to aquatic photolysis, although experimental photolytic rate data have not been located.

Many nitroaromatic compounds photolyze rapidly in sunlight producing a large number of primary and secondary products (Mill and Mabey, 1985). Nakagawa and Crosby (1974) found that an aqueous solution of 4-nitrophenol in a laboratory flask was completely degraded within 1-2 months when exposed to sunlight; hydroquinone and 4-nitrocatechol were the photolysis products. By analogy to 4-nitrophenol, photolysis of 4,6-dinitro-o-cresol could produce 2-methyl-4-nitrocatechol and 2-methyl-6-nitro-hydroquinone (Callahan et al., 1979).

The absorption of 4,6-dinitro-o-cresol to aquatic organic particulates may result in photosensitized photolysis (Callahan et al., 1979), since humic and fulvic substances in natural waters absorb sunlight strongly.

2.1.4. Microbial Degradation. Tabak et al. (1981) studied the biodegradability of 114 organic priority pollutants to determine the extent of microbial degradation and acclimation periods. The test method used was a static-culture flask-screening procedure using 5 and 10 ppm of the test pollutant, a settled wastewater inoculum, 5 ppm yeast, a mineral salts solution, and a 7-day static incubation at 25°C followed by three weekly subcultures. Under these conditions, 4,6-dinitro-o-cresol was not found to be significantly degraded; 52 and 0% degraded in 7 days (5 and 10 ppm,

respectively) and 51 and 14% degraded in 28 days (5 and 10 ppm, respectively). 4,6-Dinitro-o-cresol was also found to be not significantly degradable by the Zahn-Wellens test (Zahn and Wellens, 1980).

Mixed cultures of bacteria, adapted to phenol, were able to biodegrade 4,6-dinitro-o-cresol (100 ppm) in Warburg respirometer tests (Chambers et al., 1963; Tabak et al., 1964). Mixed bacteria cultures (primarily Pseudomonas sp.) obtained from water, mud and soil, however, were unable to degrade 4,6-dinitro-o-cresol (207 ppm) in 48-hour static flask tests. Patterson and Kodukala (1981) reported that an activated sludge system receiving an influent of 11 ppb 4,6-dinitro-o-cresol was able to degrade 99% of the compound.

4,6-Dinitro-o-cresol has been degraded by cell-free extracts of Vibrio alkaliescens (McCormick et al., 1976) and by bouillon cultures of Escherichia coli, Proteus vulgaris, Bacillus cereus and B. subtilis (Nehez et al., 1977a). In addition, 4,6-dinitro-o-cresol can be biodegraded by soil microorganisms (Section 2.3.1.), but there are insufficient data available to predict the significance of microbial degradation of the dinitrocresols in the aquatic environment.

2.1.5. Volatilization. Pertinent data regarding the volatilization of the dinitrocresols could not be located in the available literature as cited in the Appendix. Using the vapor pressure (1.05×10^{-4} mm Hg) and water solubility (130 ppm) of 4,6-dinitro-o-cresol from Table 1-2, Henry's Law constant can be estimated to be 2.1×10^{-7} atm-m³/mol, indicating that 4,6-dinitro-o-cresol essentially does not volatilize from water (Lyman et al., 1982). Since 4,6-dinitro-o-cresol ionizes substantially in water (pKa of 4.46), the above estimation of Henry's Constant is probably too high.

suggesting that the compound is even less volatile than predicted. The dinitrocresols are, therefore, not expected to volatilize from water significantly.

2.1.6. Adsorption. Weber (1972) noted that acidic-type pesticides (including 4,6-dinitro-o-cresol) can be quite mobile in aquatic systems; however, data specific to the dinitrocresols were not presented. The calculated K_{ow} for the dinitrocresols (2.564) (U.S. EPA, 1986a) indicates moderate soil mobility (Section 2.3.3.), which suggests that aquatic adsorption may not be important. Callahan et al. (1979) suggested that adsorption to clay minerals may have some significance.

2.1.7. Bioaccumulation. Although experimentally determined BCFs were not located, BCFs can be estimated by using the regression equation, $\text{Log BCF} = 0.76 \text{ Log } K_{ow} - 0.23$ (Lyman et al., 1982). Using the calculated $\text{Log } K_{ow}$ value of 2.564 (U.S. EPA, 1986a), the BCF is calculated to be ~52, which is not suggestive of significant bioaccumulation. In addition, Callahan et al. (1979) have suggested that 4,6-dinitro-o-cresol is not expected to bioaccumulate because of its marked toxicity.

2.2. AIR

2.2.1. Reaction with Hydroxyl Radical. Although experimental data were not located, the rate constant for the atmospheric reaction between 4,6-dinitro-o-cresol and OH radical has been theoretically calculated to be 3.0×10^{-11} cm³/molecule-sec at 25°C (U.S. EPA, 1986a). Assuming an average atmospheric OH radical concentration of 8×10^5 molecules/cm³, a half-life of 8 hours is calculated (U.S. EPA, 1986a).

2.2.2. Reaction with Ozone. Ozone is not expected to add to 4,6-dinitro-o-cresol in the atmosphere (U.S. EPA, 1986a) indicating that this mechanism is not important.

2.2.3. Photolysis. 4,6-Dinitro-o-cresol absorbs light of wavelength >300 nm (Callahan et al., 1979), indicating a potential for direct photolysis in the atmosphere. Rate data, however, are not available and cannot be estimated from existing absorption data. Although direct photolysis may contribute to the removal of the dinitrocresols from the atmosphere, it is probably not as important as reaction with OH radical.

2.3. SOIL

2.3.1. Microbial Degradation. Jensen (1964) examined the effects of dinitro-o-cresol at concentrations up to 150 ppm upon soil microflora in four different soil types. In neutral and mildly alkaline soils, doses of 10-150 ppm increased CO₂ output by 10-30% over control, although at ≥50 ppm, there was a lag period before stimulation. In acidic soil, only low concentrations (1-20 ppm) produced significant stimulation. Ammon and Jaeggi (1981) found that dinitro-o-cresol increases CO₂ production from soil microflora at low concentrations, but decreases it at high concentrations.

4,6-Dinitro-o-cresol has been shown to be metabolized in various pure cultures isolated from soils. Gundersen and Jensen (1956) found 4,6-dinitro-o-cresol to be degraded by Corynebacterium simplex; however, elevated concentrations of the compound became inhibitory and then toxic. Jensen (1966) found species of Arthobacter and Pseudomonas able to metabolize 4,6-dinitro-o-cresol. 4,6-Dinitro-o-cresol, present in nutrient solutions at levels of 400-500 ppm, was intensely metabolized by Clostridium perfringens A (Merenyuk, 1974). Strains of Azotobacter have been found to transform dinitro-o-cresol to 6-acetamido-2-methyl-4-nitrophenol (Wallnoefer et al., 1978). Tewfic and Evans (1966) found that in pure culture Pseudomonas degraded 4,6-dinitro-o-cresol to an amino-cresol, whereas Arthobacter initially hydroxylated the aromatic ring before catabolism proceeded further.

4,6-Dinitro-o-cresol has both insecticidal and fungicidal activity (Wallnoefer et al., 1978) suggesting that sufficiently high concentrations of the compound may be toxic to soil microorganisms. At high levels, 4,6-dinitro-o-cresol has been found to kill Azotobacter and Clostridia (Meremyuk, 1974) and to be toxic to various strains of Rhizobium (Jensen, 1969). Application of 4,6-dinitro-o-cresol to soil at recommended concentrations for herbicide uses has been shown to have no inhibitory effect on soil microflora (Corke and Robinson, 1960; Capriotti and Martini, 1959).

2.3.2. Chemical Degradation. Pertinent data could not be located in the available literature; however, Callahan et al. (1979) suggested that 4,6-dinitro-o-cresol may undergo some hydrolysis while sorbed to clay minerals.

2.3.3. Adsorption. Experimental adsorption data specific to the dinitrocresols were not located. Acidic-type pesticides (which include 4,6-dinitro-o-cresol) can be quite mobile in both soil and aquatic systems, with the greatest mobility in coarse-textured sandy soils and the least mobility in fine-textured clay and organic soils (Weber, 1972).

Table 2-1 lists various regression equations that can be used to estimate the K_{oc} of a chemical and the K_{oc} values calculated for the dinitrocresols. The K_{oc} values estimated using $\log K_{ow}$ are relatively consistent and predict moderate soil mobility for the dinitrocresols. The K_{oc} values calculated from water solubilities suggest moderate to low soil mobility.

Callahan et al. (1979) suggested that adsorption of 4,6-dinitro-o-cresol by clay may be significant.

2.3.4. Photolysis. Pertinent data could not be located in the available literature; however, surface photolysis may be possible since the dinitrocresols absorb sunlight and potential adsorption to humic substances on soil surfaces may photosensitize photolysis.

TABLE 2-1

 K_{OC} Estimation from Regression Equations for Dinitrocresols^a

Equation	Calculated K_{OC} Value
$\text{Log } K_{OC} = 3.64 - 0.55 \log \text{ water solubility (in ppm)}$	300 ^b 190 ^c
$\text{Log } K_{OC} = 0.44 - 0.54 \log \text{ water solubility (in mol fraction)}$	1260 ^b 820 ^c
$\text{Log } K_{OC} = 0.544 \log K_{OW} + 1.377$	590 ^d
$\text{Log } K_{OC} = 0.937 \log K_{OW} - 0.006$	250 ^d
$\text{Log } K_{OC} = 1.000 \log K_{OW} - 0.21$	225 ^d

^aSource: Lyman et al., 1982^b4,6-dinitro-o-cresol water solubility of 130 ppm^c2,6-dinitro-p-cresol water solubility of 290 ppm^dLog K_{OW} of 2.564 (U.S. EPA, 1986a)

2.3.5. Volatilization. The dinitrocresols are solids at ambient temperatures and have relatively low vapor pressures (10^{-4} to 10^{-3} mm Hg at 20-25°C; see Table 1-2); therefore, volatilization from dry surfaces is not expected to be rapid. In moist soils, the ionization of dinitrocresols will reduce the evaporation rate. This suggests that volatilization of the dinitrocresols from soil will not be relatively significant.

2.3.6. Persistence. Callahan et al. (1979) reported that 4,6-dinitro-o-cresol usually disappears from soil within a few weeks to 2 months. Laboratory degradation studies have shown dinitro-o-cresol to decompose in 1-3 months in soil (Jensen, 1966, 1969). Gundersen and Jensen (1956) reported an experiment in which repeated application of 4,6-dinitro-o-cresol to a soil resulted in a shortened decomposition time; this was due possibly to adaptation of the microorganisms.

2.4. SUMMARY

Sufficient experimental data were not available to predict the exact fate of the dinitrocresols in water; however, photolysis and oxidation appear to be two mechanisms by which the dinitrocresols may be measurably removed from sunlit waters. Although the biogradability of 4,6-dinitro-o-cresol has been demonstrated in mixed bacterial cultures (Chambers et al., 1963), in activated sludge (Patterson and Kodukala, 1981) and in various pure culture studies (McCormick et al., 1976; Nehez et al., 1977a; Hamdi and Tewfik, 1970; Gundersen and Jensen, 1956; Jensen, 1966; Merenyuk, 1974; Wallnoefer et al., 1978; Tewfic and Evans, 1966), the significance of biodegradation in natural waters cannot be predicted with certainty from the available data. Hydrolysis, volatilization, bioaccumulation and adsorption are not expected to be important processes, although adsorption to clay minerals may have some significance (Callahan et al., 1979).

Dinitrocresol present in the ambient atmosphere is expected to be rapidly removed by reaction with OH radical. Based on a theoretically calculated rate constant, the half-life of 4,6-dinitro-o-cresol in the atmosphere, with respect to OH radical, has been calculated to be ~8 hours (U.S. EPA, 1986a). Photolysis may have some significance as an atmospheric removal sink.

4,6-Dinitro-o-cresol usually disappears from soil within a few weeks to 2 months (Callahan et al., 1979) when applied as a herbicide. The microbial degradation of 4,6-dinitro-o-cresol in soil has been demonstrated (Jensen, 1964; Ammon and Jaeggi, 1981); a repeated application of 4,6-dinitro-o-cresol to a soil resulted in a shorter decomposition time, which may be due to microbial adaptation (Gundersen and Jensen, 1956). Based on K_{oc} estimations from regression equations (see Table 2-1), 4,6-dinitro-o-cresol is expected to have moderate to low soil mobility, which suggests that some leaching can occur. Leaching is expected to be greatest in sandy soils and minimal in clay soils.

3. EXPOSURE

3.1. WATER

4,6-Dinitro-o-cresol has been detected in the wastewaters of a pest control plant in England and in the wastewaters of a specialty chemical plant (18 ppm) (U.S. EPA, 1980a). Shackelford and Keith (1976) reported the detection of 4,6-dinitro-o-cresol (no concentration reported) in two U.S. chemical plant effluents. 4,6-Dinitro-o-cresol has also been detected in the wastewater from the Oak Ridge Gaseous Diffusion Plant (concentration or detection limit not reported) (McMahon, 1983) and in the water-sediment-soil complex at the Love Canal (concentration or detection limit not reported) (Hauser and Bromberg, 1982).

4,6-Dinitro-o-cresol was not detected in urban stormwater runoff in 15 U.S. cities during the preliminary analysis of the U.S. EPA's Nationwide Urban Runoff Program (detection limit not reported) (Cole et al., 1984). It was detected, however, in the Great Lakes ecosystem (concentration not reported) (Great Lakes Water Quality Board, 1983).

A gross analysis of data from the U.S. EPA STORET Data Base was available only for 4,6-dinitro-o-cresol (Table 3-1). No water monitoring data were located for 2,6-dinitro-p-cresol.

In addition to industrial wastewaters containing dinitrocresol, 4,6-dinitro-o-cresol may be emitted to the water environment by direct pesticidal applications or by pesticide leaching or runoff.

3.2. FOOD

Pertinent data were not located regarding the presence or absence of dinitrocresol residues in U.S. food. Since the primary pesticide use of 4,6-dinitro-o-cresol involves treatment of fruit trees during the dormant season, it is unlikely that contamination of human foodstuffs will occur to

TABLE 3-1

**Gross Analysis of Data for 4,6-Dinitro-o-cresol
from the U.S. EPA STORET Data Base***

	Water	Whole Water	Tissue (wet weight)	Sediment (dry weight)
Number of reporting stations	6110	142	632	890
Maximum concentration	250,000 µg/l	400 µg/l	1000 mg/kg	570,000 µg/kg
Minimum concentration	0	0	0	0
Mean concentration	478 µg/l	79 µg/l	28 mg/kg	7856 µg/kg

*Source: U.S. EPA, 1986b

any large extent (U.S. EPA, 1980a). Floru et al. (1977) detected 4,6-dinitro-o-cresol on Romanian plums at harvest time; however, residues were below tolerance limits. Schmidt (1970) detected 4,6-dinitro-o-cresol residues on potatoes taken from East German fields treated with the compound; the author suggested that cooking would remove most of the 4,6-dinitro-o-cresol because it is steam-volatile.

3.3. INHALATION

Occupational exposure poses the greatest risk of inhalation exposure to 4,6-dinitro-o-cresol. Workers can be exposed during manufacturing, formulating or applying the pesticide as an aerosol (U.S. EPA, 1980a). In the United States, ~3000 workers are potentially exposed to 4,6-dinitro-o-cresol (U.S. EPA, 1980a). Spraying of the compound in apple orchards can result in worker respiratory exposure of 0.03-0.13 mg/hour (Wolfe, 1976). The workplace air concentration of 4,6-dinitro-o-cresol in German facilities preparing the spray liquids was found to range from 0.081-0.846 mg/m³ (Thiele et al., 1981).

No ambient atmospheric monitoring data were located for any of the dinitrocresols. 4,6-Dinitro-o-cresol can be formed in the atmosphere by the photochemical oxidation of o-cresol with nitrogen oxides (Grosjean, 1984, 1985).

3.4. DERMAL

Risk of dermal exposure is also greatest to those workers involved in manufacturing, formulating or applying the pesticide as an aerosol (U.S. EPA, 1980a). Spraying of 4,6-dinitro-o-cresol in apple orchards can result in worker dermal exposures of 22.5-55.1 mg/hr (Wolfe, 1976).

3.5. SUMMARY

4,6-Dinitro-o-cresol has been detected in various industrial wastewater effluents (U.S. EPA, 1980a; Shackelford and Keith, 1976; McMahon, 1983) and in the water-sediment soil complex at the Love Canal (Hauser and Bromberg, 1982). No water monitoring data were located for 2,6-dinitro-p-cresol. Exposure of 4,6-dinitro-o-cresol to the water environment may result from direct pesticidal applications or by pesticide leaching or runoff. No pertinent data were located on the presence or absence of dinitrocresol residues in U.S. food. Persons at the greatest risk to inhalation and dermal exposure to 4,6-dinitro-o-cresol include workers manufacturing, formulating or applying the pesticide as an aerosol (U.S. EPA, 1980a). No ambient atmospheric monitoring data were found for any of the dinitrocresols.

4. PHARMACOKINETICS

Because no new data were found, the major portion of this Chapter is taken verbatim from a Health and Environmental Effects Profile prepared in 1984 (U.S. EPA, 1984).

4.1. ABSORPTION

Although information regarding the absorption potential of 2,6-dinitro-p-cresol in animals or humans was not located, King and Harvey (1953a) determined that 4,6-dinitro-o-cresol was readily absorbed through the gastrointestinal tract, lungs and skin of rats and rabbits following oral, inhalation and dermal administration, respectively. The rats were given a single gavage dose of 30 mg/kg and were killed at intervals after dosing. The entire gastrointestinal tract was removed and flushed of its contents. By measuring the amount of 4,6-dinitro-o-cresol in the blood, and in homogenates of the stomach, small intestine, large intestine and gastrointestinal contents, King and Harvey (1953a) determined that >80% of the dose was absorbed within 1 hour, >90% within 2 hours and >95% within 7 hours after dosing. Peak blood levels of 4,6-dinitro-o-cresol were reached within 2-4 hours of a single oral dose of 30 or 40 mg/kg to rats and 10 or 20 mg/kg to rabbits, indicating rapid absorption. Rats were also placed in a tank for up to 5 hours with a steady flow of 4,6-dinitro-o-cresol aerosol at 0.1 mg/m³. Blood levels rose steadily to ~50 µg/g blood during exposure. The investigators stated that the rats became quiescent and ingested very little food and water and displayed little tendency for licking during exposure. The lungs contained ~6-12 times more 4,6-dinitro-o-cresol than did the alimentary canal, indicating that most of the compound in the blood resulted from pulmonary absorption. The investigators also concluded that

since the fur became yellow during exposure to the aerosol, while the skin remained white, little of the compound was absorbed through the skin. Absorption did occur through the shaved skin of rabbits following topical application of 4,6-dinitro-o-cresol. Rats were not used for the skin absorption experiment because they could not be prevented from licking.

Harvey et al. (1951) administered 4,6-dinitro-o-cresol orally to five male volunteers at a dose of 75 mg/day on 5 consecutive days. Blood levels rose to 9-16 $\mu\text{g/g}$ on the last day of exposure and continued to rise to up to 22 $\mu\text{g/g}$ for 2 days after the last dose.

4.2. DISTRIBUTION

Harvey (1953) administered 20 mg/kg 2,6-dinitro-p-cresol in 0.5% NaHCO_3 solution to mice by intraperitoneal injection and found 35 ± 8.9 $\mu\text{g/g}$ in the blood 4 hours after injection, and 8 ± 0.32 $\mu\text{g/g}$ 24 hours after injection. A 75% reduction in blood levels was observed between 4 and 24 hours.

Parker et al. (1951) examined the distribution of 3,5-dinitro-o-cresol following a single subcutaneous injection of 10 mg/kg to Porton rats (group sizes not specified). The dinitrocresol content in serum, brain, spleen, kidney, liver, muscle, heart and lung was examined from 30 minutes to 6 hours following dosing. After 30 minutes it was estimated that 83% of the administered dose was in the serum and after 6 hours 72% still remained in the blood. No evidence of accumulation in the examined organs was seen.

An additional nine rats were administered 40 successive daily subcutaneous injections of 20 mg dinitrotoluene/kg. When liver, kidney and serum concentrations were compared with 19 animals that received a single injection of 20 mg/kg, no significant differences were found.

Serum half-lives were determined following a single subcutaneous injection of 10 mg dinitrocresol/kg to be 15, 20 and 36 hours in the rat, cat and dog, respectively. In view of the lack of accumulation of the compound in the tissues, along with relative persistence in the blood, the authors proposed that binding to plasma proteins could be responsible.

Evidence was obtained by King and Harvey (1953a) that some accumulation of 4,6-dinitro-o-cresol in the blood can occur in rats, but not in rabbits after repeated oral or intraperitoneal doses. Dermal application of 4,6-dinitro-o-cresol to rabbits resulted in significant quantities remaining in the blood for 48 hours after application. The authors suggested storage of the compound in the skin and subsequent release as an explanation for the much longer residence time of the compound in blood following dermal application as compared with intraperitoneal injection, peroral administration or inhalation exposure (King and Harvey, 1953a). Experiments with humans suggested that man was relatively inefficient in eliminating single or multiple doses of 4,6-dinitro-o-cresol (King and Harvey, 1953b). This conclusion was based upon the relatively slow elimination rate of the compound from blood compared with rats and rabbits, as well as from data on urinary excretion (Section 4.4.). Analysis of the blood indicated that the compound was bound to the plasma albumin fraction (King and Harvey, 1953b).

4.3. METABOLISM

Pertinent data regarding the metabolism of 2,6-dinitro-p-cresol could not be located in the available literature as cited in the Appendix. Data obtained for 4,6-dinitro-o-cresol in rabbits indicated that the compound is slowly metabolized by the reduction of the 6 nitro group and excreted in the urine.

Truhaut and Delavaur (1967) administered 4,6-dinitro-o-cresol by gavage to rabbits and found 6-amino-4-nitro-o-cresol in the liver, kidney, brain and urine. No 4-amino-6-nitro-o-cresol was detected. Smith et al. (1953) characterized the metabolism of 4,6-dinitro-o-cresol in rabbits given the compound by gavage at a dose of 20-30 mg/kg. Within 2 days after dosing, the urine contained unchanged 4,6-dinitro-o-cresol accounting for 5-5.5% of the dose, conjugates for 0.7%, derivatives of 6-amino-4-nitro-o-cresol for ~12%, 6-acetamido-4-nitro-o-cresol for 1.5% and hydroxyl group conjugates for 9-10%. The urine also contained traces of 6-amino-4-nitro-o-cresol, 4-amino-6-nitro-o-cresol and 3-amino-5-nitrosalicylic acid.

4.4. EXCRETION

Elimination of 2,6-dinitro-p-cresol from the blood of mice following a single intraperitoneal dose of 20 mg/kg was 75% complete within 24 hours after administration (Harvey, 1953).

Although no other information is available for 2,6-dinitro-p-cresol, the elimination of 4,6-dinitro-o-cresol was studied in humans after accidental exposure (during spraying), in rabbits after gavage administration of 30 mg/kg, and in rats after administration (route unspecified) of 30 mg/kg (King and Harvey, 1953b). Blood levels of 4,6-dinitro-o-cresol were measured at intervals from 3.5-144 hours after dosing. The decay of 4,6-dinitro-o-cresol levels in blood with time appeared to be monoexponential, with half-times of 154 hours for humans, 27 hours for rats and 6.6 hours for rabbits. No attempt was made to monitor metabolites. The human data were supplemented and partially confirmed by data from volunteers who received single doses of 75 mg 4,6-dinitro-o-cresol by an unspecified route. Thus, the half-time for elimination from blood was much longer for humans than for rabbits, with the value for rats being intermediate between the other two

species. In rats, the elimination rates were faster when 4,6-dinitro-o-cresol was administered by intraperitoneal injection than orally or by inhalation of an aerosol (King and Harvey, 1954). A sudden increase in environmental temperature to animals treated with 4,6-dinitro-o-cresol resulted in a great increase in the toxic action but only a slight increase in the elimination rate of 4,6-dinitro-o-cresol (Harvey, 1959; King and Harvey, 1954).

Twenty-four hours after the administration by an unspecified route of a single 75 mg dose of 4,6-dinitro-o-cresol to humans, <2% of parent compound was detected in the urine. During the 13 days after dosing, 7% of the administered 4,6-dinitro-o-cresol was excreted (King and Harvey, 1953b). No attempt was made to monitor metabolites. Urinary excretion rates for the rabbit showed that 5-8% of the administered (unspecified route) doses (34.4, 41.5, 41.2 or 44.6 mg/kg) appeared in the urine within the first 5 hours, and thereafter the amount excreted was small, ~1% over 7 days (King and Harvey, 1953b). Urinary excretion per day in the rat was similar to man. Only ~2% of the dose administered to the rat was excreted within 96 hours after single doses of 5.75, 7.0 or 6.0 mg/kg 4,6-dinitro-o-cresol by an unspecified route (King and Harvey, 1953b). At 24 hours after dosing, an average of ~40% of the administered 4,6-dinitro-o-cresol was present in blood and urine of humans (primarily in the blood). The remaining 60% was unaccounted for, but no attempt was made to identify metabolites. Fecal elimination and, hence, the possibility of biliary excretion was not investigated. No other information was reported.

4.5. SUMMARY

Pertinent data regarding the pharmacokinetics and metabolism of 2,6-dinitro-p-cresol could not be located in the available literature as cited in

the Appendix. 4,6-Dinitro-o-cresol is rapidly absorbed through the skin, the respiratory system and the gastrointestinal tract (King and Harvey, 1953a). Rats absorbed >90% of an orally administered dose within 7 hours. Based on blood elimination curves it appears that humans and rats, but not rabbits, may accumulate some 4,6-dinitro-o-cresol (King and Harvey, 1953b). Half-lives for elimination were 154 hours for humans, 27 hours for rats and 6.6 hours for rabbits. The accumulation was attributed to the ability of the compound to bind to plasma protein rather than to accumulate in organs. This is supported by the work of Parker et al. (1951) that showed little 3,5-dinitro-o-cresols in the tissues of rats at various times after dosing. No direct evidence is available for the other isomers. In rabbits, 4,6-dinitro-o-cresol was metabolized primarily to 6-amino-4-nitro-o-cresol and hydroxy group conjugates (Smith et al., 1953; Truhaut and DeLavaur, 1967). These metabolites were excreted in the urine. Elimination of the compound occurs more rapidly following injection rather than oral administration, and excretion patterns of humans vs. experimental animals are substantially different. King and Harvey (1953b) suggested that the slow elimination of 4,6-dinitro-o-cresol from humans could be due to either storage in a tissue depot or slow detoxification or excretion of the compound. They felt that storage in the tissues was less probable, supported by the Parker et al. (1951) rat data and data from two fatal human poisonings showing little dinitrotoluene in the tissues (details not described).

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of dinitrocresols could not be located in the available literature as cited in the Appendix. The isomers are not scheduled for testing by the National Toxicology Program (NTP, 1986).

5.2. MUTAGENICITY

The available information regarding the mutagenicity of dinitrocresols are summarized in Table 5-1. The results reported are inconsistent and limited experimental detail was given. Sundvall et al. (1984) reported positive results for 4,6-dinitro-o-cresol in Salmonella typhimurium strains TA98, TA100 and TA1538. Mutagenicity was decreased in the presence of S-9. The same author reported positive results for 2,6-dinitro-p-cresol in strain TA100 of S. typhimurium. Nishimura and Oshima (1983) and Nishimura et al. (1982) reported mutagenicity for 4,6-dinitro-o-cresol only in S. typhimurium strain TA98 in the presence of metabolic activation. Somani et al. (1981) reported a positive response in the TA100 strain but not TA98 for the 4,6-dinitro-o-cresol. Anderson et al. (1972) reported no mutagenicity for 4,6-dinitro-o-cresol when tested in eight strains of S. typhimurium. Nehez et al. (1977b, 1978a,b, 1980, 1994) observed increases in chromosome aberrations in human lymphocytes and mouse bone marrow when treated with a herbicide containing 50% 4,6-dinitro-o-cresol (Krezonit E). Positive responses were also reported with the same herbicide in human leukocytes (Selyes and Paldy, 1978), in a dominant lethal test in mice (Nehez et al., 1978c) and in recessive lethal mutations in Drosophila melanogaster (Haberzetti and Mueller, 1979; Mueller and Haberzetti, 1979).

TABLE 5-1

Mutagenicity Testing of Dinitrocresols

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	<i>Salmonella</i> Typhimurium TA98, TA100, TA1535, TA1538	commercial grade 4,6-dinitro- o-cresol	plate incorporation	0, 100, 200 µg/plate	±S-9	±	Positive in TA98, TA100, TA1538; the mutagenicity was decreased in presence of S-9.	Sundvall et al., 1984
Reverse mutation	<i>S. Typhimurium</i> TA98, TA100	commercial grade 2,6-dinitro- p-cresol	plate incorporation	0, 100, 200 µg/plate	±S-9	±	Positive results in TA100; the mutagenicity was reduced in the presence of S-9.	Sundvall et al., 1984
Reverse mutation	<i>S. Typhimurium</i> TA98, TA100	4,6-dinitro- o-cresol (purity NR)	NR	NR	±S-9	±	Positive in the presence of S-9 in TA98.	Mishimura and Oshima, 1983; Mishimura et al., 1982
Reverse mutation	<i>S. Typhimurium</i> TA98, TA100, TA1537	technical grade 4,6-dinitro- o-cresol	spot test	50 µl of 1000 µg/ml	none	+	Mutagenic in TA100 but not TA98 and TA1537.	Somani et al., 1981
Reverse mutation	<i>S. Typhimurium</i>	technical grade 4,6-dinitro- o-cresol	agar overlay	NR	none	-	Negative in eight strains.	Anderson et al., 1972
Chromosome aberrations	human lymphocytes	50% 4,6-di- nitro-o-cresol (Krezonite E)	culture	0.02, 0.2 and 2 µg/ml	none	+	56.5%, 53.7 and 74.5% of aberrant cells, respec- tively.	Mehez et al., 1977b, 1978a,b, 1980, 1984
Chromosome aberrations	mouse bone marrow (strain NR)	50% 4,6-di- nitro-o-cresol	<i>in vivo</i>	single dose of 20 mg/kg, 10-day subchronic doses of 10 mg/kg	NA	+	Aberrations seen in 75, 76, 88 and 95% of marrow cells.	Mehez et al., 1977b, 1978a,b, 1980, 1984
Chromosome aberrations	germ cells of male C57BL mice	50% dinitro- o-cresol	<i>in vivo</i>	0.6 mg/kg 2 times/week for 5 weeks	NA	-	No significant increase in the number of chromo- somal abnormalities.	Mehez et al., 1982
Chromosome aberrations	human leukocyte	50% 4,6-di- nitro-o-cresol	culture	NR	none	+	Mutagenic	Selyes and Palley, 1978

TABLE 5-1 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Recessive lethal mutation	<u>Drosophila</u> <u>melanogaster</u>	4,6-dinitro- o-cresol/ purity NR	<u>in vivo</u>	50-200 ppm	MA	+	0.6% lethal mutations but the frequency for the negative control was not reported.	Haberzetti and Mueller, 1979; Mueller and Haberzetti, 1979
Dominant lethal	CFLP mice	4,6-dinitro- o-cresol/ purity NR	<u>in vivo</u>	10 mg/kg	MA	+	Germ cells damaged in pre- and post-meiotic phase of spermatogenesis.	Mehez et al., 1978c

*A herbicide containing 50% dinitro-o-cresol

NR - Not reported; MA - not applicable

Nehez et al. (1981) reported an increase in chromosome damage in cells from embryonic mouse liver from embryos whose dams were exposed to the herbicide Krezonit E (50% dinitro-o-cresol) every other day during the second third, but not the first third, of gestation. A dose of 5 mg/kg was given by gavage in saline. Numbers of litters per group were not reported.

5.3. TERATOGENICITY

Results of a teratogenicity study on the effect of a herbicide containing 50% 4,6-dinitro-o-cresol (Krezonit E) are reported in Table 5-2 (Nehez et al., 1981). Groups of DBA and ABJ-H mice were treated independently either on days 4, 9 or 11 or continuously during days 11-14 of pregnancy. At the dosages applied, the herbicide had no teratogenic effect on the DBA or ABJ-H strain of mice. In addition to the results in Table 5-2, there were no significant differences in corpora lutea/dam, implantation/dam, live embryos/dam, resorbed embryos/dam and percent preimplantation loss. In another experiment when pregnant CFLP mice were treated during the first week or days 9-12 of pregnancy, no embryotoxic or teratogenic effects were observed; however, a significant increase in chromosome aberrations was seen when the herbicide was administered during days 9-12 of pregnancy.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of the isomers of dinitrocresol could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Information regarding chronic and subchronic toxicity were found only for 4,6-dinitro-o-cresol.

TABLE 5-2
Teratogenicity Testing of Krezonit E (50% Dinitro-o-cresol)^{a,b}

Route	Species/ Strain	No. of Dams at Start	Daily Dose or Exposure (mg/kg)	Treatment Days	Observation Days	Fetal Response
Intraperitoneal	mice/DBA	10	15	day 11 of pregnancy	day 18 of pregnancy	12.66% postimplantation loss; mean weight of embryos (1.08 g) and ratio of malformations (6%) did not differ significantly from negative control group.
Intraperitoneal	mice/DBA	31	15	days 4, 9 and 11 of pregnancy	day 18 of pregnancy	10.76% postimplantation loss; (1.11 g) mean weight of embryos; (0.5%) malformations did not differ significantly from control group.
Oral	mice/DBA	13	0	days 11-14 of pregnancy	day 18 of pregnancy	7.84% postimplantation loss; (1.08 g) mean weight of embryos; (1%) malformations did not differ significantly from control group.
None (control)	mice/DBA	20	0	NA	day 18 of pregnancy	6.04% postimplantation loss; (1.14 g) mean weight of embryos; (1%) malformations
Intraperitoneal	mice/ABH-J	12	15	days 4, 9 and 11 of pregnancy	day 18 of pregnancy	12.86% postimplantation loss; 1 g mean weight of embryos; 1% malformations did not differ signifi- cantly from control group.
Intraperitoneal	mice/ABH-J	16	15	days 4, 9 and 11 of pregnancy	day 18 of pregnancy	10.26% postimplantation loss; 1.01 g mean weight of embryo; 1% malformations did not differ significantly from control group.
None (control)	mice/ABH-J	66	0	NA	day 18 of pregnancy	12.12% postimplantation loss; 1.03 g mean weight of embryo; 1% malformations
Oral	mice/CFLP	NR	5 (4 doses)	1st 1/3 of pregnancy	day 16 of pregnancy	No chromosome aberration in embryos.
Oral	mice/CFLP	NR	5	days 9-12 of pregnancy	day 16 of pregnancy	Significant increase in chromosome aberrations.

^aSource: Mehoz et al., 1981

^bMaternal response was not reported.

5.5.1. Human Effects. In addition to its use in agriculture, 4,6-dinitro-o-cresol was used as a substitute for dinitrophenol in the 1930s for the treatment of obesity. Its use was discontinued after several individuals suffered from cataracts, blindness and even death.

Dodds and Robertson (1933) orally administered 4,6-dinitro-o-cresol to average weight and overweight volunteers in an attempt to establish a safe dosage for humans. An unspecified number of volunteers were given 3 mg/kg/day for 4 days. By the 3rd day of treatment, the BMR had increased by 50% and by as much as 100% on the 4th day of treatment. Signs and symptoms of toxicity observed were profuse sweating, lethargy, headache, appetite loss and greenish-yellow pigmentation of the conjunctivae. Volunteers returned to normal after treatment was stopped. A second group of volunteers was given one 3 mg/kg oral dose and observed for several days. A 20-30% increase in BMR was reported within 24 hours and returned to normal in 4-5 days. A third group of volunteers were given 0.5-1.0 mg/kg/day for an unspecified period. The authors reported that no toxic effects were observed at this dosage and that it was the dosage needed to maintain a BMR 30-50% greater than normal. Harvey et al. (1951) reported lassitude, headache, malaise and staining of the conjunctivae in five male humans ingesting 75 mg/day dinitro-o-cresol for 5 days.

Ibrahim et al. (1934) reported adverse effects in 15 (8 men and 7 women) overweight people who consumed 50 or 100 mg/day of dinitro-o-cresol for 7 weeks. A few days after initiation of treatment, all subjects developed signs and symptoms of intoxication, including excessive sweating, thirst, fatigue, decreased appetite, elevated BMR and greenish-yellow conjunctivae. Plotz (1936) reported similar symptoms in three persons who ingested 0.35-1.5 mg/kg/day of dinitro-o-cresol for up to 9 weeks for purposes of

weight reduction. In a case reported by Quick (1937), a woman developed cataracts and blindness after ingesting an unspecified dose of the compound for 3 years. Horner (1942), however, reviewed 13 case reports of cataracts in patients taking 4,6-dinitro-o-cresol at doses recommended for weight reductions.

In addition to the deaths and adverse effects that resulted from the use of dinitro-o-cresol for weight reduction purposes, severe intoxication and death have been documented in occupational exposure situations (NIOSH, 1978). Although many case reports from agricultural and industrial exposure report that the compound is toxic to humans when inhaled, very few document exposure levels or link effects to exposure (NIOSH, 1978; U.S. EPA, 1980a). In general, symptoms of inhalation exposure to dinitro-o-cresol are similar to those reported from oral exposure, except that cataracts have not been documented as a result of inhalation exposure. A report from the Russian literature lists effects in the cardiovascular, gastrointestinal and CNS and changes in blood counts in workers exposed to 0.7 and 0.9 mg/m³ of the compound (Burkatskaya, 1965). Fairhall (1957) reported severe toxic effects in a worker exposed to 4.7 mg/m³ dinitro-o-cresol. The worker recovered when the exposure was decreased to 2.5 mg/m³.

5.5.2. Animal Effects. Spencer et al. (1948) reported on the effects of long-term oral administration of 4,6-dinitro-o-cresol to male rats. The rats were fed 0.01, 0.02, 0.05 and 0.1% (100, 200, 500 or 1000 ppm) of the compound in the diet for periods up to 181 days. No adverse effects were observed at the 100 ppm level in any of the parameters studied, including mortality, body weight, food consumption, organ weights, hematological values, BUN and histopathological changes. Significant decreases in weight gain, food consumption and organ weights were observed at the 200 ppm level.

Marked decreases in weight gain and food consumption, depletion of body fat and elevated BUN were noted at the 500 ppm dietary level. When the compound was fed at 1000 ppm for 10 days, the rats did not eat; there was rapid weight loss and 50% of the rats died. No histopathological changes were observed at any dose level and no rats developed cataracts.

Ambrose (1942) maintained groups of 5-10 male Wistar rats on diets containing a chemical, which he identified as 3,5-dinitro-o-cresol and stated was a synonym for 4,6-dinitro-o-cresol, at 0, 0.00078, 0.00156, 0.00312, 0.00625, 0.0125, 0.025, 0.05 or 0.1% (0, 7.8, 15.6, 31.2, 62.5, 125, 250, 500 or 1000 ppm) for up to 105 days. No effects on growth or food consumption were observed in rats treated at ≤ 31.2 ppm. At 62.5 and 125 ppm, food consumption and growth were increased above control, while growth and food consumption were markedly inhibited at >250 ppm. The rats treated at 500 and 1000 ppm refused the diet and died within a few days. At 125 ppm, 60% of the rats died during the experiment. Gross and histological examination of unspecified visceral organs revealed no treatment-related lesions.

Twenty male and 20 female Wistar rats were given 4,6-dinitro-o-cresol in the diet at 0, 50, 100, 200 or 400 mg/kg food (ppm) for 90 days (Den Tonkelaar et al., 1983). At doses >200 ppm, mortality was increased, food intake, growth and food efficiency decreased, and protein and creatinine in the urine decreased. At the 100 ppm level, growth and food efficiency were decreased and ketones and creatinine were noted in the urine. In the blood, an increase in hemoglobin, hematocrit, MCV/MCH and urea were observed at levels >100 ppm. At 400 ppm only, leukocyte and lymphocyte counts were decreased, SGPT activity was increased and the protein content in the blood was decreased. Blood glucose was increased at levels >200 ppm. A dose-related decrease in pyruvate and T_3 was observed at all levels. T_4 was

also reduced at all levels but not in a dose-related manner. The activity of liver glucose-6-phosphate dehydrogenase was markedly decreased at 400 ppm and to a lesser extent at 100 and 200 ppm. The absolute organ weights of the thymus, pituitary, ovaries, heart and thyroid were markedly decreased at the 400 ppm level and were lower than controls at the 200 ppm level. At 400 ppm, the relative weights of the heart, brain, liver, kidney, spleen, adrenals (males only) and thyroid were increased, while those of the thymus, uterus, ovaries, testes and prostate gland were decreased. At the 200 ppm level, increases in the relative weights of the brain, liver and kidneys were noted. At the 100 ppm level, only an increase in the liver weights was noted. At the lowest concentration (50 ppm), no changes in the absolute or relative organ weights, no changes in most clinical parameters measured and no effect on growth, mortality, body temperature or food intake and efficiency were noted. The only changes reported at the low dosage were appearance of ketones in the urine and decreased pyruvate, T_3 and T_4 levels in the blood. Pyruvate and T_3 were decreased in a dose-related manner (Den Tonkelaar et al., 1983). No mention of cataract development in treated rats was made.

Limited information from the Russian literature on inhalation exposure of animals identified 0.001 mg/m³ (continuous exposure) as a no effect level for rats (Popov et al., 1971), 0.2 mg/m³ (4 hours/day, 2-3 months) as a minimal effect level for cats and 2 mg/m³ (4 hours/day, 2-3 months) as a toxic level for cats (Burkatskaya, 1965).

5.6. OTHER RELEVANT INFORMATION

Dinitro-o-cresol is an uncoupler of oxidative phosphorylation, which accounts for its high acute toxicity in mammals (NIOSH, 1978; Ilivicky and Casida, 1969). Oral LD₅₀ values range from 30-85 mg/kg in rats and 16.4-47 mg/kg in mice (U.S. EPA, 1980a).

4,6-Dinitro-cresol was screened for possible immunotoxic properties and was found to cause no effects or marginal effects on the immune system. Male Wistar rats were exposed to diets containing 4,6-dinitro-o-cresol at 25, 100 or 400 mg/kg diet (ppm) for 3 weeks. The immune parameters evaluated were weights and histology of the thymus, spleen, mesenteric and popliteal lymph nodes, peripheral lymphocyte and monocyte counts, and serum IgM and IgG levels (Vos et al., 1983).

5.7. SUMMARY

Pertinent data regarding the carcinogenicity of isomers of dinitrocresol could not be located in the available literature; the isomers have not been scheduled for testing by the National Toxicology Program (NTP, 1986).

Inconsistent results have been reported for mutagenicity testing (see Table 5-1). Anderson et al. (1972) reported negative results for 4,6-dinitro-o-cresol when tested without activation in eight strains of S. typhimurium; however, positive results without activation were reported for 4,6-dinitro-o-cresol in S. typhimurium strains TA98, TA100 and TA1538 and for 2,6-dinitro-p-cresol in strain TA100; addition of S-9 reduced the mutagenicity (Sundvall et al., 1984). Nishimura and Oshima (1983) and Nishimura et al. (1982) reported mutagenicity for 4,6-dinitro-o-cresol in strain TA98 in the presence of metabolic activation, whereas Somani et al. (1981) reported a positive response without metabolic activation in strain TA100 but not TA98. Positive responses were observed for a herbicide containing 50% 4,6-dinitro-o-cresol (Krezonit E) when tested in human lymphocytes, mouse bone marrow (Nehez et al., 1977b, 1978a,b, 1980, 1984), dominant lethal test in mice (Nehez et al., 1978c) and recessive lethal test in Drosophila (Haberzettl and Mueller, 1979; Mueller and Haberzettl, 1979).

No embryotoxic or teratogenic effects were observed in the offspring of DBA or ABH-J mice treated orally or intraperitoneally with 8-15 mg/kg of the herbicide (Krezonit E) containing 50% dinitro-o-cresol during gestation (Mehez et al., 1981). Increases in chromosome aberrations of the embryos were observed when Krezonit E was administered orally to CFLP mice in the first few days of pregnancy.

Information regarding the effects of oral administration of 4,6-dinitro-o-cresol to humans is available since this compound was used in the treatment of obesity. Toxic effects, which included elevated BMR, excessive sweating, thirst, fatigue, decreased appetite and greenish-yellow conjunctivae, were reported when 0.35-1.5 mg/kg/day was ingested for periods up to 9 weeks (Plotz, 1936; Ibrahim, 1934). Similar but less pronounced symptoms developed when the compound was given in similar dosages for a few days (Harvey et al., 1951; Dodds and Robertson, 1934). When the compound was given at 3 mg/kg/day, marked signs of toxicity developed and the BMR was elevated by 100% on the 4th day of treatment. These effects disappeared when treatment was discontinued (Dodds and Robertson, 1933). Deaths from overdoses and blindness resulting from formation of bilateral cataracts have been reported (NIOSH, 1978; U.S. EPA, 1980a). Neither dose-response information nor duration of treatment associated with cataract formation was specified in the literature. In a case report by Quick (1937), cataract formation resulting in blindness was reported in a woman who ingested the compound for 3 years at an unspecified dosage.

When 4,6-dinitro-o-cresol was administered in the diets of rats at 0, 0.01, 0.02, 0.05 and 0.1% for periods up to 181 days, no compound-related effects were observed at the 0.01% level. At the 0.02% level, significant decreases in weight gain, food consumption and organ weight occurred.

Marked toxicity developed at the 0.05 and 0.1% levels (Spencer et al., 1948). Ambrose (1942) reported no effects at a level of 62.5 ppm in rats fed the compound for 105 days; however, at a level of 125 ppm, 60% of the rats died. Many compound-related effects were observed in rats at dietary levels of 100, 200 and 400 ppm for 90 days (Den Tonkelaar et al., 1983). Effects on mortality, food intake and efficiency, growth, hematological changes, changes in clinical chemical parameters in blood and urine, and changes in absolute and relative organ weights were noted at levels ≥ 100 ppm and were more severe at the highest level. The only effects noted when the compound was given at 50 ppm was the presence of ketones in the urine, and a reduction in pyruvate, T_3 and T_4 levels. Pyruvate and T_3 were reduced in a dose-related manner (Den Tonkelaar et al., 1983). Cataract formation was not observed or mentioned in the animal studies (Spencer et al., 1948; Den Tonkelaar et al., 1983).

Case reports from occupational exposure have shown the compound to be toxic to humans when inhaled (NIOSH, 1978; U.S. EPA, 1980a); however, few reports link effects with exposure levels. In general, symptoms from inhalation exposure appear to be similar to those resulting from oral exposure. Cataract formation has not been documented in humans or animals as a result of inhalation exposure.

6. AQUATIC TOXICITY

6.1. ACUTE

The available information concerning acute toxicity of 4,6-dinitro-o-cresol to freshwater fishes is summarized in Table 6-1. The limited data suggest that salmonids may be more sensitive than other species. The two lowest reported acutely toxic concentrations are 0.066 mg/l and 0.200 mg/l for rainbow trout, Salmo gairdneri, and Atlantic salmon, Salmo salar, respectively (Johnson and Finley, 1980; Zitko et al., 1976). Bluegills, Lepomis macrochirus, are also quite sensitive, with 96-hour LC₅₀ values of 0.230-0.360 mg/l (Buccafusco et al., 1981; Johnson and Finley, 1980). Data for other dinitrocresol isomers or for marine fish species could not be located in the available literature as cited in the Appendix.

Data concerning acute toxicity of dinitrocresols to aquatic invertebrates are presented in Table 6-2. The only data available for 2,4-dinitrocresol (LeBlanc, 1980) indicate that it is about equally toxic to Daphnia magna as 4,6-dinitro-o-cresol. The lowest reported acutely toxic concentration was 0.012 mg/l 4,6-dinitro-o-cresol, which was the toxicity threshold for inhibition of cell multiplication in the ciliate protozoan, Uronema parduczi (Bringmann and Kuehn, 1981). Data concerning the acute toxicity of dinitrocresols to marine invertebrates could not be located in the available literature as cited in the Appendix.

6.2. CHRONIC

The only data concerning chronic effects of dinitrocresols were provided by Slooff and Canton (1983) and are presented in Table 6-3. Duration of these experiments and the dinitrocresol isomer(s) used were not specified. The lowest threshold concentration reported was 0.032 mg/l, which was a NOEC for effects on reproduction of the snail, Lymnaea stagnalis.

TABLE 6-1
Acute Toxicity of Dinitrocresols to Fishes

Species	Isomer	Concentration (mg/L)	Effect	Reference
Rainbow trout <u>Salmo gairdneri</u>	4,6	0.066 0.25-0.30	96-hour LC50 lethal, 12-19 hours	Johnson and Finley, 1980 Van Hoof, 1980
Atlantic salmon <u>Salmo salar</u>	4,6	0.200	lethal threshold	Zitko et al., 1976
Fathead minnow <u>Pimephales promelas</u>	4,6 4,6 4,6 4,6 4,6	8.6 1.9-2.2 1.3-1.7 2.2 1.7	48-hour LC50 (static) 96-hour LC50 (flowthrough) 92-hour LC50 (flowthrough) LC50 lethal threshold (14- to 18-day LC50)	Phipps et al., 1981 Phipps et al., 1981 Phipps et al., 1981 Alexander et al., 1983 Alexander et al., 1983
Minnows (unspecified)	4,6	1.5-4.0	overturned	McKee and Wolf, 1963
Bluegill <u>Lepomis macrochirus</u>	4,6	0.360 0.230	96-hour LC50 96-hour LC50	Johnson and Finley, 1980 Buccafusco et al., 1981

TABLE 6-2

Reference

TABLE 6-3

Subchronic NOECs for Various Species Exposed to Dinitro-o-cresol*
(unspecified isomers)

Species	NOEC (mg/l)	Effect
FISH		
Guppy <u>Poecilia reticulata</u>	1.0	mortality, behavior, growth
Medaka <u>Oryzias latipes</u>	0.1	mortality, behavior
INVERTEBRATES		
Water flea <u>Daphnia magna</u>	1.0	mortality, reproduction
Mosquito <u>Culex pipiens</u>	10.0	mortality and growth
Snail <u>Lymnaea stagnalis</u>	1.0 0.032	mortality, hatching reproduction
Hydra <u>Hydra oligactis</u>	0.32	growth
AMPHIBIANS		
Tadpole <u>Xenopus laevis</u>	0.32	mortality, growth, development

*Source: Slooff and Canton, 1983

6.3. PLANTS

Limited information is available concerning toxicity of 4,6-dinitro-o-cresol to aquatic plants. Huang and Gloyna (1968) reported that 10 mg/l caused "substantial toxicity" in terms of reduced chlorophyll in Chlorella pyrenoidosa. Bringmann and Kuehn (1978) reported toxicity thresholds for inhibition of cell multiplication in Microcystis aeruginosa and Scenedesmus quadricauda of 0.15 and 13.0 mg/l, respectively.

There are some data concerning effects of dinitrocresol on bacteria. A concentration of 10 mg/l dinitrocresol (unspecified isomer) adversely affected Salmonella sp., Streptococcus faecalis and Pseudomonas aeruginosa (Aleshnya and Tsatska, 1979). The toxicity threshold for inhibition of cell multiplication of Pseudomonas putida was 16 mg/l (Bringmann and Kuehn, 1980).

6.4. RESIDUES

Pertinent data regarding dinitrocresol residues in aquatic organisms could not be located in the available literature as cited in the Appendix.

6.5. SUMMARY

Limited information is available concerning toxicity of dinitrocresols to aquatic organisms. Most of the data pertained to 4,6-dinitro-o-cresol. The lowest reported acutely toxic concentration was 0.066 mg/l, a 96-hour LC_{50} for rainbow trout (Johnson and Finley, 1980). Salmonid fishes and bluegills appeared to be more sensitive to 4,6-dinitro-o-cresol than minnows (see Table 6-1). Among invertebrates, the lowest reported acutely toxic concentration was 0.012 mg/l 4,6-dinitro-o-cresol, the toxicity threshold for the ciliate protozoan Uronema parduczi (Bringmann and Kuehn, 1981). The LC_{50} values for 2,4-dinitrocresol (LeBlanc, 1980) and 4,6-dinitro-o-cresol

(Bringmann and Kuehn, 1977) indicated a similar level of toxicity to Daphnia magna. No additional data for dinitrocresols other than the 4,6-isomer were found and no data for marine fish and invertebrates were located.

Slooff and Canton (1983) provided chronic toxicity data for unspecified dinitrocresols. Chronic effects in several fish and invertebrates generally occurred at concentrations close to those causing acute toxicity. The lowest threshold in this study was 0.032 mg/l, a NOEC for reproductive effects in snails.

Among the plant species tested, the most sensitive was the blue-green alga, Microcystis aeruginosa, with a toxicity threshold of 0.15 mg/l (Bringmann and Kuehn, 1978).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

A TWA-TLV of 0.2 mg/m³ has been adopted by ACGIH (1985) for 4,6-dinitro-o-cresol. The TLV is followed by a "skin" notation, indicating that the dermal route contributes substantially to the overall exposure. The TLV is considered to be below the threshold for debilitating symptoms (ACGIH, 1980). NIOSH (1978) also recommended that the Federal workplace environmental limit be 0.2 mg/m³, which is the current Permissible Exposure Limit (OSHA, 1985). NIOSH (1978) indicated that the lowest exposure level that resulted in toxic effects was 0.7 mg/m³.

An ADI of 0.39×10^{-3} mg/kg/day was determined by U.S. EPA (1980a) based on the standard recommended by NIOSH (1978). The ADI was determined assuming an 8-hour workday, an average inhalation volume of 28.6 l/minute (NIOSH, 1978), comparable rates of respiratory and gastrointestinal absorption and using an uncertainty factor of 100.

The National Academy of Science Drinking Water Limit is 1 µg/l (U.S. EPA, 1985a).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of dinitrocresol could not be located in the available literature as cited in the Appendix.

B. RISK ASSESSMENT

Pertinent data regarding the carcinogenicity of isomers of dinitrocresol could not be located in the available literature as cited in the Appendix. Inconsistent results have been reported for mutagenicity testing (see Table 5-1). Embryotoxic and teratogenic effects were not observed in mice treated with a herbicide containing 50% dinitro-o-cresol (see Table 5-2). Since evidence of carcinogenicity has not been demonstrated, it is appropriate to derive an ADI using oral exposure data.

Spencer et al. (1948) fed male rats 4,6-dinitro-o-cresol at dietary levels of 100, 200, 500 or 1000 ppm (5, 10, 25 or 50 mg/kg/day assuming that a rat consumes a daily amount of food equal to 5% its body weight) for periods up to 182 days. No effects on survival, body or organ weights, urea nitrogen or histopathological changes were observed at the 5 mg/kg/day dose given for 182 days. Significant decreases in weight gain, food consumption and organ weights were reported at all other doses (10, 25 and 50 mg/kg/day). Rats treated at 25 mg/kg for 77-82 days also exhibited elevated BUN and decreased body fat. Rats were fed the highest dose for 10 days only because they refused to eat, lost weight rapidly and 50% of the rats died. Ambrose (1942) reported no effects at a level of 63 ppm (3.15 mg/kg/day) in rats fed the compound for 105 days; however, at a level of 125 ppm (6.25 mg/kg/day), 60% of the rats died. In another study, Wistar rats were administered the compound in the diet at 0, 50, 100, 200 or 400 ppm (0, 2.5, 5, 10 or 20 mg/kg/day) for 90 days (Den Tonkelaar et al., 1983). Toxic effects were observed at doses of ≥ 5 mg/kg. These effects included decreased growth, increased mortality, changes in absolute and relative organ weights, blood cell changes and changes in clinical chemical parameters. At the low

dosage of 2.5 mg/kg/day, no effects on growth, mortality or absolute and relative organ weights were observed. The only effects found at this dosage were decreases in T_3 , T_4 and pyruvate. Pyruvate and T_3 were decreased in a dose-related manner, while T_4 was reduced by the same amount for all dosages.

Effects at dosages ranging from 0.35-3 mg/kg/day have been reported in humans (Plotz, 1936; Ibrahim et al., 1934; Harvey et al., 1951; Dodds and Robertson, 1933). Doses of 0.35-1.5 mg/kg/day for up to 9 weeks have been used for weight reduction (Plotz, 1936; Ibrahim et al., 1934), with the reported effects including elevated BMR, excessive sweating, fatigue and thirst, and greenish-yellow conjunctivae. Within 4 days of administration, severe toxic effects were reported at a dosage of 3 mg/kg/day; when use of the compound was terminated, the symptoms disappeared (Dodds and Robertson, 1933). One case of chronic (3-year) exposure to the chemical resulted in cataract formation and blindness (Quick, 1937); however, the dosage for this effect was not reported. Horner (1942), however, reviewed case reports of cataracts in patients taking 4,6-dinitro-o-cresol at doses recommended for weight reduction.

Since carcinogenicity data for the dinitrocresols were not available, it is appropriate to derive an ADI based on toxicity data. Although several subchronic dietary studies of 4,6-dinitro-o-cresol in rats were available, they are not appropriate for the ADI derivation for several reasons. As indicated by species differences in accumulation in blood levels and elimination from blood (see Chapter 4), the potential for chronic intoxication appears to be much greater for humans than for rats. Furthermore, treatment of patients with 4,6-dinitro-o-cresol at oral doses recommended for weight

reduction has been associated with cataract formation. The formation of cataracts was not reported for rats exposed to the compound in the diet for ≤ 180 days.

As stated in Section 7.1., an ADI has been derived for 4,6-dinitro-o-cresol using the TLV and occupational exposure limit of 0.2 mg/m^3 . In one derivation (U.S. EPA, 1980b), an ADI of $0.39 \times 10^{-3} \text{ mg/kg/day}$ was determined by assuming an 8-hour workday, an average inhalation volume of 28.6 L/minute (NIOSH, 1978), comparable rates of respiratory and gastrointestinal absorption and using an uncertainty factor of 100. If the exposure was expanded over a 7-day week, the ADI would be $0.28 \times 10^{-3} \text{ mg/kg/day}$.

If the ADI is to be based on the TLV, it is recommended that the U.S. EPA (1980b) reference breathing volume of $10 \text{ m}^3/8\text{-hour day}$, the 5/7 day adjustment and an uncertainty factor of 100 be used. If gastrointestinal and pulmonary absorption are considered to be equal, the ADI would be $0.2 \times 10^{-3} \text{ mg/kg/day}$; if an absorption factor of 0.5 is applied, the ADI would be $0.1 \times 10^{-3} \text{ mg/kg/day}$.

Although not chronic, human oral exposure information is available and may be preferred over the inhalation TLV for derivation of an ADI based on oral exposure, because oral exposure has been associated with cataract formation while inhalation exposure has not. A LOAEL of 0.35 mg/kg/day resulting in elevated BMR, excessive sweating, fatigue and thirst, and discoloration of the conjunctivae was identified when the compound was given for 9 weeks (Plotz, 1936). It might be assumed that similar dosages could have been ingested by patients who developed cataracts since they were taking the compound at doses recommended for weight reductions (Horner, 1942). Dosages $>1 \text{ mg/kg/day}$ have been shown to produce severe toxic symptoms (Harvey et al., 1951; Dodds and Robertson, 1933). Using a LOAEL of

for 9 weeks (Plotz, 1936). It might be assumed that similar dosages could have been ingested by patients who developed cataracts since they were taking the compound at doses recommended for weight reductions (Horner, 1942). Dosages >1 mg/kg/day have been shown to produce severe toxic symptoms (Harvey et al., 1951; Dodds and Robertson, 1933). Using a LOAEL of 0.35 mg/kg/day (Plotz, 1936) and dividing an uncertainty factor of 1000 results in a provisional ADI of 0.35×10^{-3} mg/kg/day. The uncertainty factor of 1000 was based on using 10 for the uncertainty of using a LOAEL, 10 for the uncertainty associated with the exposure period (9 weeks) and 10 for the range of sensitivities in humans.

This value is very close to, and hence supports, the estimate based on the TLV that utilizes an absorption factor of 50% (0.1×10^{-3} mg/kg/day). The data base is limited with the complication that there appears to be a greater than usual divergence in the sensitivity of humans versus the common animal models. It is suggested that the most conservative estimate, 0.1×10^{-3} mg/kg/day, be utilized as an interim ADI. The ADI is now most often referred to as the Reference dose (RFD).

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Pertinent data regarding the effects of subchronic and chronic oral exposure and inhalation exposure of 4,6-dinitro-o-cresol in animals and humans are discussed in Section 5.5. and summarized in Table 9-1. No data were found for 2,6-dinitro-p-cresol.

9.1.1. Inhalation. Many case reports from occupational exposure (agricultural) have shown 4,6-dinitro-o-cresol to be toxic to humans when inhaled (NIOSH, 1978; U.S. EPA, 1980a). Signs and symptoms from inhalation exposure are similar to those resulting from oral exposure, except that cataract formation was not observed. Most case reports fail to report or relate exposure levels to effects and are of no value in the development of an RQ classification. A Russian study reported that occupational exposure levels of 0.7 and 0.9 mg/m³ produced symptoms (Burkatskaya, 1965). Fairhall (1957) reported an exposure level of 4.8 mg/m³ to be toxic in one individual and a level of 2.5 mg/m³ as a level where all symptoms disappeared. The only animal inhalation data found was also from the Russian literature and identified 0.001 mg/m³ as a no-effect level continuously for 2 months for rats (Popov et al., 1971), 0.2 mg/m³, 4 hours/day for 2-3 months as a minimal effect level for cats and 2 mg/m³, 4 hours/day as a toxic level for cats (Burkatskaya, 1965). Equivalent doses were not calculated for these exposures because the contribution to the total dose by dermal absorption, which is considerable (ACGIH, 1986), cannot be estimated.

9.1.2. Oral. Spencer et al. (1948) administered 4,6-dinitro-o-cresol to male rats in the diet at 0, 100, 200, 500 or 100 ppm (0, 5, 10, 25 and 50 mg/kg/day) for periods up to 182 days. No effects were seen at 5 mg/kg/day.

TABLE 9-1
Toxicity Summary for Dinitro-o-cresol

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg) ^a	Vehicle/ Physical State	Purity	Exposure	Dose (mg/kg/day)	Response	Reference
Oral	human	MR	MR	70, >70	MR	MR	daily for 4 days	3	By day 3 an increase in BMR by 50%; by day 4, an increase in BMR by 100%. Profuse sweating, lethargy, headache, loss of appetite and greenish- yellow pigmentation of the conjunctivae.	Dodds and Robertson, 1933
Oral	human	MR	MR	70, >70	MR	MR	daily/duration MR	0.5-1.0 ^b	Elevation in BMR by 30-50%. No other signs of toxicity specified.	Dodds and Robertson, 1933
Oral	human	MR	MR	70, >70	MR	MR	single dose	3 mg/kg	BMR elevated 20-30% within 24 hours; BMR normal in 4-5 days. No other signs of toxicity reported.	Dodds and Robertson, 1933
Oral	human	BM 7F	15	over- weight	MR	MR	50 or 100 mg/day for 7 weeks	0.6-1.3 ^c (male) 0.7-1.4 ^c (female)	All developed excessive sweat- ing, thirst, fatigue, decreased appetite, elevated BMR, greenish-yellow conjunctivae.	Ibrahim et al., 1934
Oral	human	MR	3	over- weight	MR	MR	daily for 9 weeks	0.35-1.5 ^b	Excessive sweating, fatigue, thirst, elevated BMR, decreased appetite, greenish-yellow conjunctivae.	Plotz, 1936
Oral	human	F	MR	over- weight	MR	MR	3 years	MR	Cataracts and blindness.	Quick, 1937
Oral	human	M	5	70	capsule	pure	75 mg/day for 5 days	0.92-1.27 ^b	Lassitude, headache, malaise, staining of conjunctivae	Harvey et al., 1951
Inhalation	human	MR	1	70	MR	MR	4.7 mg/m ³ occupational	ME	Fever, elevated BMR, excessive sweating, cough, shortness of breath, rapid pulse and respi- ration.	Fairhall, 1957
Inhalation	human	MR	1	70	MR	MR	2.5 mg/m ³ occupational	ME	Above signs of toxicity dis- appeared at this dose.	Fairhall, 1957

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg) ^a	Vehicle/ Physical State	Purity	Exposure	Dose (mg/kg/day)	Response	Reference
Inhalation	human	NR	NR	70	occupa- tional (agri- culture)	NR	0.7 mg/m ³	NE	Slight changes in blood and autonomic nervous system, isolated complaints.	Burkatskaya, 1965
Inhalation	human	NR	NR	70	occupa- tional (manu- facturing)	NR	0.9 mg/m ³	NE	Cardiovascular, CNS and gastrointestinal effects, changes in blood count.	Burkatskaya, 1965
Oral	rats/ albino	M	20	0.26 ^d	diet	NR	0.01% in diet for 182 days (100 ppm)	5e	No effect on survival, body or organ weights, hematologic values or BUN; no histopathologic changes.	Spencer et al., 1948
Oral	rats/ albino	M	20	0.25 ^d	diet	NR	0.02% in diet for 181 days (200 ppm)	10e	Significant decrease in weight gain, decreased food consumption, decreased organ weights.	Spencer et al., 1948
Oral	rats/ albino	M	22	0.20 ^d	diet	NR	0.05% in diet for 77-82 days (500 ppm)	25e	Marked decrease in weight gain and food consumption, depletion of body fat, elevated BUN.	Spencer et al., 1948
Oral	rats/ albino	M	20	0.16 ^d	diet	NR	0.1% in diet for 10 days (1000 ppm)	50e	Rapid weight loss, refusal to eat, ~50% mortality.	Spencer et al., 1948
Oral	rats	NR	NR	0.35	diet	NR	63 mg/kg and 125 mg/kg for 105 days	3.15e 6.25	No observable effect at the low dose; at high dose, 60% of animals died.	Ambrose, 1942

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg) ^a	Vehicle/ Physical State	Purity	Exposure	Dose (mg/kg/day)	Response	Reference
Oral	Wistar rats	10M 10F	20	0.06	diet	NR	0, 50, 100, 200 and 400 ppm, 90 days.	0, 5, 10, 20 and 40 ^e	At doses >100 mg/kg, food efficiency and growth were decreased. No effect at low dose. Mortality were increased at 200 and 400 ppm. The only urinary parameter increased at the low dose was ketone. No blood cell changes were observed at the low dose. Pyruvate and T ₃ were decreased in a dose- related manner, while T ₄ was reduced the same for all doses. No changes in liver enzymes were noted at the low dose and no changes in absolute or relative organ weights were observed at this dose.	Den Tonkelaar et al., 1983
Inhalation	cats	NR	3	3 ^f	aerosol of solution	NR	0.2 mg/m ³ 4 hours/day, 2-3 months (head exposure)	NE	Transient changes in blood cell counts, peroxidase and catalase activities, slight increase in body temperature.	Burkatskaya, 1965
Inhalation	cats	NR	3	3 ^f	solid aerosol	NR	2 mg/m ³ 4 hours/day, 2-3 months (head exposure)	NE	Blood changes, weight loss, labored breathing, sluggish- ness. Two died.	Burkatskaya, 1965
Inhalation	rats	NR	NR	0.35	NR	NR	0.001 mg/m ³ continuous, 2 months	NE	No effects noted on clinical chemistry or behavior.	Popov et al., 1971

^aAssumed unless otherwise stated.^bDosage reported by investigator.^cEstimated assuming a body weight of 80 kg for males and 70 kg for females because the patients were overweight.^dEstimated from growth curve.^eAssuming a rat will eat the equivalent of 5% of its body weight in food.^fReference body weight from U.S. EPA (1985b)

NR = Not reported; NE = not estimated because contribution to overall dose by dermal absorption cannot be quantified

Significant decreases in weight gain, food consumption and organ weights were observed at doses of ≥ 10 mg/kg/day. Severe toxicity occurred at 50 mg/kg/day and the treatment was discontinued in 10 days. Ambrose (1942) observed no effect in rats administered the compound at 63 ppm (3.15 mg/kg/day) for 105 days; however, 60% of the animals treated at 125 ppm (6.25 mg/kg/day) died. Den Tonkelaar et al. (1983) observed male and female Wistar rats fed 0, 50, 100, 200 and 400 ppm (0, 2.5, 5, 10 and 20 mg/kg/day) dinitro-o-cresol for 90 days. At doses of ≥ 5 mg/kg/day, food efficiency and growth were decreased, blood cell changes were observed, and changes in absolute and relative organ weights were noted. No effects on growth, food efficiency, blood cells or absolute and relative organ weights were observed at the 2.5 mg/kg/day dose. Levels of pyruvate and T_3 were decreased in a dose-related manner and T_4 was uniformly decreased at all doses. The studies by Spencer et al. (1948) and Ambrose (1942) could not be used for derivation of an RQ since the effects observed related primarily to the marked decrease in food consumption. No specific histopathological effects were observed at any dose level and none of the rats were reported to have developed cataracts. The study by Den Tonkelaar et al. (1983), however, could be used for derivation of an RQ. In this study, blood and urine were collected for hematological and clinical-chemical parameters, and mortality, food consumption, and growth were evaluated. In addition, 29 organs and tissues were weighed and evaluated histopathologically. The effects observed were not attributed to inadequate food intake. From this study, the dose of 2.5 mg/kg/day could be used for RQ derivation. Since the study is of 90-day duration this dose should be divided by an uncertainty factor of 10. Multiplying the 0.25 mg/kg/day dose by the cube root of the body weight ratio approximation (using 0.35 kg as the reference weight of

the rat divided by 70 kg as the reference weight of man) and subsequently multiplying by 70 kg gives human MED of 3.0 mg/day, corresponding to a RV_d of 4.8 (Table 9-2). An RV_e rating of 1 was assigned since the effects of decreased pyruvate, T_3 and T_4 were biochemical in nature and were not accompanied by any pathological or organ weight changes. Multiplying the RV_d by the RV_e results in a CS of 4.8, which corresponds to an RQ of 5000.

Human oral exposure data are available since the compound was administered for weight reduction purposes (see Table 9-1). Doses of 0.35-1.5 mg/kg/day for periods of 5 days to 9 weeks resulted in elevated BMR, excessive sweating, thirst and fatigue, decreased appetite and greenish-yellow conjunctivae (Plotz, 1936; Harvey et al., 1951; Ibrahim et al., 1934; Dodds and Robertson, 1933). By the 4th day of treatment, doses of 3 mg/kg/day resulted in severe toxic symptoms, which disappeared when the treatment was discontinued (Dodds and Robertson, 1933). Quick (1937) reported a case of cataract development resulting in blindness in one individual who ingested the compound for 3 years. The dosage for this effect was not reported, but Horner (1942) reviewed 13 case reports of cataracts in patients taking doses recommended for weight reduction. Therefore, it might be assumed that the doses were similar to those reported by Plotz (1936). Using this assumption, an RQ from human exposure data could be derived. Taking the LOAEL of 0.35 mg/kg/day, multiplying by an assumed body weight of 70 kg and dividing by 10 to convert to a chronic value results in a human MED of 2.45 mg/day (see Table 9-2). The MED corresponds to an RV_d of 4.9. If it is assumed that cataract formation and subsequent blindness may result from the same dosage as the other effects, then an RV_e of 8 is warranted since this effect is irreversible and results in loss of function. Multiplying the

TABLE 9-2
Composite Scores for Oral Toxicity of Dinitro-o-cresol

Species	Dose (mg/kg/day)	Chronic Human MED* (mg/day)	RV _d	Effect	RV _e	CS	RQ	Reference
Human	0.35	2.45	4.9	Elevated BMR, excessive sweating, fatigue and thirst, decreased appetite, pigmentation of conjunctivae; assume this was approximate dosage that caused cataracts and blindness in Quick (1937).	8	39.2	100	Plotz, 1936; Quick, 1937
Rat	2.5	3.0	4.8	Decreased pyruvate, T ₃ and T ₄ .	1	4.8	5000	Den Tonkelaar et al., 1983

*The dose was divided by an uncertainty factor of 10 to approximate chronic exposure.

RV_d by the RV_e results in a CS of 39.2, which corresponds to an RQ of 100. Since the individuals were overweight, it could be argued that a body weight of >70 kg should be used. If a body weight of 80 kg for overweight individuals is used instead of 70 kg, the RQ will still correspond to 100. An RQ of 100 for 4,6-dinitro-o-cresol (Table 9-3) is recommended since adequate human data are available and since the highest CS for oral exposure results from these data. In a previous determination of the RQ (U.S. EPA, 1983) the same data were used. Data were insufficient to derive an RQ for 2,6-dinitro-p-cresol (Table 9-4).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Information regarding the carcinogenicity of dinitrocresols could not be located in the available literature as cited in the Appendix. Therefore, according to the IARC classification scheme, isomers of dinitrocresol are group 3 chemicals, that is, they cannot be classified as to their carcinogenicity for humans. According to the CAG classification (U.S. EPA, 1984b) these chemicals are placed in Group E, that is, no data are available and other criteria for ranking must be used.

TABLE 9-3

4-6,Dinitro-o-cresol

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose:	2.45 mg/day
Effect:	Elevated BMR, excessive sweating, thirst and fatigue, decreased appetite, pigmentation of conjunctivae. Assume the dose-effect leads to cataracts and blindness.
Reference:	Plotz, 1936; Quick, 1937; Horner, 1942
RV _d :	4.9
RV _e :	8
Composite Score:	39.2
RQ:	100

TABLE 9-4

2-6,Dinitro-p-cresol

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:

Dose:

Effect:

Reference:

RV_d:

RV_e:

Composite Score:

RQ: Data are insufficient for derivation of an RQ

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

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IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

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Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

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